Remarks

Claims 1-13 are pending in the application, and claims 1-13 are rejected. By the present amendment, claims 1, 4, 8, 10, 12 and 13 are amended and claims 7 and 11 are canceled. The specification is amended herein to comply with U.S. formatting requirements. No new matter has been added. A marked-up copy of the Substitute Specification showing the changes made is enclosed herewith.

Claim for Foreign Priority Under 35 U.S.C. §119(a)-(d)

The present application claims priority to Austrian patent application no. A 1267/2002 filed August 23, 2002 and receipt is acknowledged in the Office Action of the papers filed under 35 U.S.C. §119(a)-(d). A typographical error was made on the Declaration, which references "A 2167/2002" instead of --A 1267/2002--. Pursuant to 37 CFR 1.76(b)(6), a Supplemental Application Data Sheet is enclosed herewith to correct this error. A request for corrected filing receipt is also enclosed.

Objections to the Drawings

In the Office Action, the drawings were objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include reference numeral "2" in Fig. 2, which reference sign was mentioned in the description at page 7, last paragraph, second line.

Fig. 2 has been amended herein by submission of a replacement drawing sheet which includes Figs. 1 and 2. In Fig. 2, reference numeral "2" has been added. No new matter has been added. It is submitted that the drawings are in compliance with the statute. Applicants respectfully request that the objection be withdrawn.

Objection to the Claims

The recitation of "measurement the electrodes" in claim 4 has been objected to due to clarity. Claim 4 is amended herein and the phrase "measurement the electrodes" has been deleted. Additional changes are made within claim 4 for clarity. No new

matter has been added. In light of the instant amendment, applicants respectfully request that the objection be withdrawn.

Rejections Pursuant to 35 U.S.C. §112, Second Paragraph

Also in the Office Action, claims 1-13 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In support of the instant rejection, the Examiner asserted there is insufficient antecedent basis for the limitation "the flow measuring cell" in line 1 of claim 1 and line 2 of claim 10, and the limitation "systems for continuous measurement" in lines 1-2 of claim 4. Claims 1 and 10 are amended herein and "the flow measuring cell" has been replaced with --a flow measuring cell--. Claim 4 is also amended herein and the phrase "systems for continuous measurement" has been deleted. No new matter has been added.

Claims 12 and 13 were also rejected under §112, second paragraph, as being indefinite for claiming both an apparatus and the method steps of using the apparatus. The references to independent claim 1 was a typographical error. Claims 12 and 13 are amended herein and now each depend from claim 10, which is directed to a method. Applicants submit that the claims as amended herein are in compliance with the statute, and respectfully request that the rejection be withdrawn.

Rejections Pursuant to 35 U.S.C. §103(a)

Claims 1-2 and 7-13 are rejected under 35 U.S.C. §103(a) as being unpatentable over Pace et al. (U.S. 5,284,568) in view of Beaty et al. (U.S. 6,645,368). It is asserted in support of the instant rejection that although Pace does not explicitly disclose the measurement voltage to be essentially a DC voltage, nor the simultaneous application of the alternating and measurement voltage, it would have been obvious to one of ordinary skill in the art to have modified the device of Pace to include a DC measurement voltage and simultaneous application of alternating and measurement voltages as taught by Beaty because as Beaty explains the measurement voltage enables concentration determination of a medically significant component of a biological

fluid (*citing*, col. 4, lines 14-21) while the AC impedance permits monitoring the position of a sample and any other interferrent present (*citing*, col. 7, lines 35-44), such as an air bubble.

Claim 7 is cancelled herein and its subject matter has been incorporated into independent claim 1. Consequently, claim 1 as amended herein recites a device for monitoring a medical microsample in a flow measuring cell of an analyzer comprising at least one electrode system comprising at least two single electrodes positioned within the flow measuring cell, and a circuit for producing the voltages to be applied to the single electrodes. The electrode system is configured for measurement of at least one substance contained in the microsample by application of a measurement voltage which is essentially a DC voltage, and detection of absence of bubbles and/or positioning of the microsample by application of an alternating voltage to the flow measuring cell. Both the alternating voltage and the measurement voltage are simultaneously and directly applied to the single electrodes of the respective electrode system, and the measured AC component or the measured impedance provides a measure for the position of the microsample and the absence of bubbles. The circuit has a summation point at which the alternating voltage for the purpose of monitoring the medical microsample with regard to position and absence of bubbles is superposed on the DC voltage serving as measurement voltage.

Claim 11 is also cancelled herein and its subject matter has been incorporated into independent claim 10. Claim 10 as amended herein recites a method for monitoring a medical microsample in a flow measuring cell of an analyzer comprising providing an analyzer including a flow measuring cell and a device comprising at least one electrode system, each system comprising at least two single electrodes; introducing a microsample into the flow measuring cell, the microsample passing the electrode system; measuring at least one substance contained in the microsample by applying a measurement voltage to the flow measuring cell, which measurement voltage is essentially a DC voltage; and detecting the absence of bubbles and/or

position of the microsample in an area of the at least one electrode system by applying an alternating voltage to the flow measuring cell simultaneous with the measurement voltage via two single electrodes of the at least one electrode system, and detecting the AC component or impedance measured.

The present invention provides that both the alternating voltage and the measurement voltage are simultaneously and directly applied to the single electrodes of the respective electrode system. In accordance with one embodiment, the alternating voltage – for example, for measuring impedance or conductance – is coupled in via two single electrodes of the electrode system that are already used for measuring a substance contained in the sample. Such simultaneous measurement offers the advantage that a change in the sample taking place during analyte measurement (e.g., gas formation at the working electrode, change in pH value, etc.) may be monitored via the simultaneous conductance measurement at the exact point in time of the analyte measurement. Moreover, repetitive measurements of microsamples with short cycle times can be carried out with high precision and reliability, and the occurrence of gas bubbles can be recognized immediately during the measurement process and may thus be taken into account. The possibility to determine the position of the sample during measurement permits a substantial reduction in sample volume as compared with state-of-the-art methods, an advantage which becomes increasingly important as the number of analytes to be measured increases.

By the Examiner's own admission, Pace et al. do not disclose the simultaneous application of the alternating and measurement voltage. In contrast, Pace et al. discloses a disposable using electrodes or elements for sample measurement and <u>different</u> electrodes or elements for bubble measurement. As recited at col. 3, line 61ff:

> *The <u>sensing elements 52</u>, which are comprised of the layers 62, 64, 66 and 68 (Fig. 5), may generally be disposed in banks or rows of linearly disposed sensor elements 52 (Fig. 1) with the sensor elements performing a reference function being on one side or row and the sensor elements performing a detection or measuring function for the analyte on the other*

> *side or row. A ground element 54, which may be in the form of a printed silver layer or other suitable metal electrode, is formed at the end of the parallel banks of sensor elements 52. Similarly a bubble sensing element 56, which is in the form of an electrically conductive metal electrode of suitable materials such as silver, is provided at the beginning or entrance of each row of sensing elements 52.*

Also, in col. 5, lines 5 to 12 of Pace et al.:

> *The electrical connectors 82 are connected to electronic circuitry 96 which may as needed incorporate a multiplexer and electrometer amplifiers to selectively connect to the various pairs of sensing elements 52, ground elements 54 and bubble sensing element 56 so as to facilitate the various differential and bubble to ground measurements necessary for the operation of the device.*

Further in col. 6, lines 43 to 48:

> *The presence of air bubbles in the flow channel 70a and 70b between the bubble sensing element 56 and the ground element 54 can be determined by measuring the impedance Z (Fig. 6) of the fluid between these elements.*

Pace et al. do not disclose that measurement voltage and alternating voltage are coupled in or applied simultaneously (i.e., via sensing elements 52) for measurement. Pace et al. instead employ an additional element or electrode (i.e., bubble sensing element 56) for bubble detection. As the Examiner further noted, Pace et al. do not disclose the measurement voltage is essentially a DC voltage. In addition, Pace et al. do not disclose an electrode system configured for detection of positioning of a microsample, either by application of an alternating voltage or any other means (col. 3, lines 61-68 of Pace et al., which is referenced in the Office Action at page 6, line 1, merely discloses the orientation of sensor elements 52), nor does Pace et al. disclose a summation point for superposing DC voltage and alternating voltage, as required by the present application.

The disclosure of Beaty et al. however does not fulfill the deficiencies of Pace et al. The '368 patent to Beaty et al. was cited in the instant application as co-pending WO 99/32881 (*see*, para. [003]):

> *From WO 99/32881 a one-way measuring cell is known which avoids the above disadvantage by applying an alternating voltage to the measuring electrodes themselves. It is possible in this way to check the exact positioning of the sample as a first step and then to proceed to the measurement itself or to reject the sample if the positioning is found to be at fault. Furthermore, flow cells with a multitude of electrode systems are known, which are suitable for a series of measurements or for continuous measurement and which determine the concentration of diverse analytes in a sample. Conditions in flow cells of this sort differ fundamentally from those in one-way cells. It is for instance not sufficient in this type of flow cells to check the positioning of the sample prior to measuring, as it will of course change during the measurement process. A further problem occurs if electrochemical reactions due to the measurement voltage cause bubble formation at an electrode, which is undesirable and may result in measurement errors.*

Beaty et al. teach away from the instant application, in that they describe a <u>one-way measuring cell</u> and not a device for monitoring a medical microsample in a flow measuring cell of an analyzer. As recited in para. [002] of the instant application:

> *In measuring medical samples a fundamental distinction is made between <u>one-way sensors</u> and <u>flow measuring cells</u>. In the case of a one-way sensor the sample is introduced into the sensor and brought into contact with measuring electrodes. The basic requirement for an accurate and error-free measurement is a suitable positioning of the sample in the measuring cell. It is a known procedure to check the positioning via special measuring contacts, to which an AC voltage is applied, such that an impedance measurement will produce a signal which provides information regarding the position of the sample. Due to the distance between the electrodes for the measurement proper and the electrodes for position-checking, errors in the measurement result may occur.*

Beaty et al. do not disclose a device or method for monitoring a medical microsample in a flow measuring cell of an analyzer comprising an electrode system configured for detection of absence of bubbles and/or positioning of the microsample by application of

an alternating voltage to the flow measuring cell. In contrast, Beaty et al. "discovered that measurement of the real component or the imaginary component, or both, of the AC impedance of an appropriately designed biosensor provides reasonable insight into sample temperature and the concentrations of certain physical and chemical interferrents." (col. 5, lines 48ff). In further contrast, Beaty et al. use the impedance measurement to determine the filling level of a <u>one-way measuring cell</u> – not the position of the microsample in a flow measuring cell. With respect to claim 7, which is cancelled herein and its subject matter incorporated into amended claim 1, it is asserted that "it would have been obvious to one of ordinary skill in the art to have modified the device of Pace et al. to include the summation point as taught by Beaty et al. because it enables the discrete determination of concentration of components in the medical sample while also allowing for the monitoring of the presence of sample or bubbles as taught by Beaty et al. (*citing*, col. 9, lines 8-17). Beaty et al. however does not fulfil the deficiencies of Pace et al., as Beaty et al. does not disclose a circuit having a summation point for at which the alternating voltage for the purpose of monitoring the medical microsample with regard to position and absence of bubbles is superposed on the DC voltage serving as measurement voltage.

Neither Pace et al. nor Beaty et al., alone or in combination, can be relied upon in support of the instant rejection, as neither reference discloses all of the limitations recited in independent claims 1 and 10, as amended herein. For all of the reasons set out above, applicants respectfully submit that the Examiner has not presented a *prima facie* case of obviousness.

Claims 3 and 4 are rejected under 35 U.S.C. §103(a) as being unpatentable over Pace et al. in view of Beaty et al. as applied to claim 1, and further in view of U.S. Patent No. 4,511,659 to Matson. Claims 5 and 6 are also rejected under §103(a) as being unpatentable over Pace et al. in view of Beaty et al. and Matson as applied to claim 3, and further in view of U.S. Patent No. 7,022,218 to Taniike et al. Claims 3-6 contain all of the limitations of the base claim from which they depend. Accordingly, for

all of the reasons set out above, applicants submit that the Examiner has not presented a *prima facie* case of obviousness and respectfully request that the rejection be withdrawn.

Applicants note the remaining prior art cited in the Office Action (U.S. Patent Nos. 3,811,841 to Kassel, 4,929,426 to Bodai et al., 5,130,009 to Marsoner et al., 5,763,795 to Tanaka et al., 6,447,657 to Bhullar et al., 6,544,393 to Künnecke, 6,723,216 to Taagaard et al., and 6,872,299 to Kermani et al.). As that additional art is not applied by the Examiner against the claims of this application, applicants are not providing any comments concerning the same at this time.

Conclusion

Applicants respectfully submit that the present application is in condition for allowance. The Examiner is encouraged to contact the undersigned to resolve efficiently any formal matters or to discuss any aspects of the application or of this amendment. Otherwise, early notification of allowable subject matter is respectfully solicited.

Respectfully submitted,
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